Chapter 3

Improving clinical trials: Unlock the power of productivity through protocol design

Executive Summary:

Protocol design has a profound impact on how efficiently and effectively a clinical trial is operated. Efforts to simplify and streamline the trial requirements can reduce the burden on enrolled participants and trial investigators, while reducing costly and time-consuming protocol deviations. By some industry estimates, 30–40% of trial failures can be attributed to problems within the original protocol design.[1] This article reviews specific opportunities to improve trial protocols in ways that reduce trial complexity. These efforts demonstrably improve key productivity metrics related to budget, timeline, footprint, and overall quality. The recommendations discussed here also improve outcomes for all interested parties—drug sponsors, clinical professionals, patients, and their support networks. Meanwhile, better protocol design improves overall trial effectiveness by showcasing the full benefit of the drug with the strongest evidence to support the clinical claims.

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The clinical trial protocol is a critical, centralized, and standardized document that describes the study objective(s), design, scientific methodology, statistical considerations, and organization of a clinical trial, while also spelling out the inclusion and exclusion criteria. The goal is to ensure that consistency is maintained across sites. A well-designed trial protocol helps to safeguard data integrity and ensures that the trial findings are reproducible and statistically reliable. However, not all protocols are written in ways that enable the trial to be as successful as possible.

A poorly designed protocol increases the risk profile for the trial and may lead to protocol amendments which are costly, disruptive, and have a direct impact on the trial's ability to meet critical productivity objectives related to timeline, budget, and quality. It also has the potential to undermine both clinical and commercial objectives that the drug developers and healthcare community were expecting.

The goal is to anticipate as many issues as early as possible during protocol development. Amendments must be reviewed and approved by regulatory agencies and Institutional Review Boards (IRBs) to ensure ongoing patient safety and compliance—so the process directly impacts trial budgets and timelines.

One of the biggest sources of risk in any clinical trial is the ability to recruit and retain the right number of trial participants to ensure that the cohort size will enable the clinical findings to have statistical viability. Specifically, undue burden on patients (which can often be avoided by more thoughtful initial protocol design) makes it hard to recruit participants and keep them engaged for the full trial duration. For example, when proper consideration is not given to the level of visit and assessment burden placed on a participant, the success of patient recruitment and retention efforts may be undermined.

A critical—yet often overlooked—way to address this problem is to design the protocol in ways that directly reflect the experiences and challenges that patients and their support network face on a day-to-day basis. By understanding the clinical endpoints that are most relevant to them, and using knowledge of specific experiences and challenges, a more effective and less burdensome protocol can be developed.

This article—the 3rd in a multi-chapter series from Fortrea that is dedicated to driving productivity in clinical trials*—discusses the most common pitfalls associated with protocol design and provides recommendations for designing protocols that deliver bottom-line productivity improvements.

* All chapters in Fortrea's productivity series can be found at **www.fortrea.com/insights**

Table 1.

Common sources of design flaws in clinical trial protocols

Failures related to market-based realities—These include lack of forethought to endpoint needs. For instance, careful consideration must be given—up front—to whether or not there is an adequate market for the drug, and whether the prevailing standard of care may prevent strong market uptake for the new therapy. Inclusion of endpoints that can help to differentiate the product (in terms of safety, efficacy, side effects profile, how the product may fit in with prevailing health plans, and more) can yield valuable insights that can then be leveraged later by the global market-access team. These specific details should be established up front in the trial protocol.

Inadequate attention to patient-centricity—This includes issues related to inclusion/exclusion criteria, failure to consider patient-specific issues, and challenges to reduce the burden, cost and discomfort, inappropriate instruments, recruitment issues, adherence challenges, patient retention, and more.

Excessive or burdensome site requirements—These include failure to appropriately streamline site requirements to reduce the burden on investigators and their clinical staff, excessive safety burdens, and more.

Design-efficiency failures—Looking at the trial design through a sustainability and carbon-footprint lens can help to identify opportunities to improve productivity. For instance, such considerations may help protocol designers to improve timelines and reduce unnecessary site visits, reduce sampling overlaps, and more. Efforts to streamline such activities provides opportunities to reduce waste for both trial investigators and patients (that is, waste related to redundant or inefficient tasks, time, logistics, travel, and wasted materials). This is discussed in greater detail below.

Incorrect assumptions for the primary endpoint—This would result in under-powered studies that don't recruit enough subjects. This common pitfall can be resolved by a robust review of the literature, prior clinical trial results, and other drugs in the class or by additional interventions approved by regulatory agencies.

Why it matters

As noted, when protocols are designed to meet important performance benchmarks, the effort improves efficiency, productivity, and pays dividends in many ways:

- **Improved inclusion/exclusion criteria:** This helps the drug sponsor and its contract research organization (CRO) partner to develop the most realistic and actionable inclusion and exclusion criteria, to set the trial up for success in terms of timely and efficient patient recruitment and startup
- **Increased participant retention:** This reduces trial participant dropouts (and thus the need to continuously recruit to backfill trial enrollment)
- **More efficient operation:** This helps the drug sponsor and its CRO partner to conduct the trial in the most operationally efficient manner, across multiple sites worldwide
- **Delivering to goals:** This puts interested parties (including the drug sponsor, CRO, trial investigators, and clinical staff) in a better position to meet critical benchmarks related to budget, timeline, clinical outcomes, and quality metrics
- **Better overall trial experience:** This reduces frustration by reducing or eliminating toil for trial investigators as well as burden, cost, and discomfort for trial participants and caregivers
- **Timely site activation and enrollment:** This allows for more timely site activation and enrollment and thus optimizes overall trial timelines, which helps to avoid budget overruns
- **Reduced protocol deviations:** This reduces or eliminates protocol deviations, which are costly and disruptive for all stakeholders
- **Better participant experience:** This facilitates a positive patient experience of clinical research driving them to become better advocates

Meanwhile, shorter timelines provide welcome clinical benefit in the broader healthcare community, as patients and healthcare providers (HCPs) are waiting for potentially lifesaving or life-improving therapies. For some patients, those time horizons are limited.

Similarly, streamlining trial execution also provides bottom-line business benefits too, as faster, more efficient clinical trials allow approved therapies to enter the market more quickly. This allows drug developers to begin recouping their development investment sooner and free up resources for other investment opportunities.

Some drug sponsors may underestimate the sheer complexity of the process of protocol design. Experienced and thoughtful approaches are needed to recognize and reconcile the specific issues that can undermine the productivity and success of the trial. Fortunately, many best practices are emerging to make protocol design even more robust and to help reduce risk and drive productivity.

It is important to note that for emerging biotech companies and startups, having a well-designed trial protocol—one that sets the trial up for success from a productivity standpoint—provides another valuable benefit. It makes the therapeutic asset a more valuable acquisition or licensing target (while potentially reducing its risk profile). This helps to strengthen the company's overall exit strategy.

To ensure that the protocol is written in a way that efficiently and effectively serves the needs of both the drug sponsor and the trial participants, it is helpful to consider key definitions from the ICH E6 (R3) as guiding principles.[2] These include the concepts of:

Quality by design—The quality of the clinical trial should be identified prospectively. This involves focusing on the critical factors of the trial in order to maximize likelihood of the trial meeting its objectives.

Fit for purpose approaches (proportionate and risk-based)—The trial processes should be proportionate to the risks inherent in the trial and the importance of the information collected. The approaches should be implemented in the way that is proportionate to the risks of the trial participants.

The stakes are high

By some industry estimates, 30–40% of trial failures can be attributed to problems within the original protocol design.[1]

Mean procedures per visit have risen from an average of 11 in the years 2009-2011 to almost 14 in 2020. Study visit lengths are therefore also rising. In 2014 around 17% of visits require more than two hours on site—fast forward to 2022 and nearly 50% of visits require more than two hours.* Such complexity invariably leads to cost and time escalation which could be avoided with a more streamlined trial protocol.

Similarly, another study suggests that 80% of data developed in Phase III trials is never used by the drug sponsor because it is not truly valuable from a clinical, regulatory, or commercial standpoint.[3] Such wasted effort creates an obvious drag on overall trial productivity. This underscores the need to embrace Adaptive Clinical Trial designs that allow modifications to the trial and/or statistical procedures of the trial after its initiation. The ultimate purpose is to make clinical trials more flexible and efficient without undermining the validity and integrity of the data.

* **Author's note:** These statistics were presented by Ken Getz, Executive Director of the Tufts Center for the Study of Drug Development and Professor at the Tufts University School of Medicine, in a presentation given at the Society for Clinical Research Sites (SCRS) in September 2024, citing the 2024 Tufts CSDD Impact Report.

Streamline trial requirements with patient centricity in mind

In recent years, a growing emphasis on the importance of understanding the needs of the patient (and their support network)—and then using such insights to inform and streamline the trial requirements—has borne fruit. The goal is to develop a more compassionate trial ecosystem to alleviate the burden for all stakeholders. While it's easy to say, it's harder to do.

As noted, for trial participants, excessive or complex trial requirements can hinder recruitment efforts and exacerbate dropout rates. Meanwhile, smaller sites with limited personnel may be unable to participate in a trial that has an overly complex protocol or burdensome trial requirements, thereby limiting opportunities for patients in those regions. And when recruitment thresholds cannot be maintained, the need to extend enrollment efforts over time—in order to ensure the statistical viability for the trial findings—further extends the burden on trial teams and drives up costs while extending trial timelines.

A more-streamlined trial protocol can help reduce both the number of logistical and administrative steps and the sheer volume of paperwork. Automating specific tasks (where appropriate) can greatly reduce the workload and burnout. This has the additional benefit of allowing clinical personnel to focus more on patient care.

Similarly, the use of digital tools for data collection and monitoring (such as approved wearable devices, smart phones, and portable monitoring systems), and the incorporation of decentralized trial sites as options within the trial protocol can help to reduce time and travel burdens. Collectively, these improvements offer direct options for making the trial experience less burdensome for patients and their caregivers.

In some cases, in an effort to drive continuous improvement and bring best practices to bear on the protocol design process, forward-thinking sponsors can work closely with their CRO partners to conduct "dry run" visits to inform the protocol development. Such an exercise can help to anticipate bottlenecks and potentially overlooked challenges and inform a more patient-friendly and streamlined protocol. For example, the team should work to understand whether patients are able to understand overly complex consent forms and participate in other requirements of the trial itself.

Table 2.

Recommendations to guide protocol design

All stakeholders—patients, sites, and sponsors—benefit from a more streamlined trial protocol, and it leads to a more efficient overall trial. Here are some recommendations. When carried out at scale—at multiple sites across the globe—these efforts will translate into considerable savings in terms of labor, budget, and timeline.

Lean into concepts of human-centered design: Allow the protocol to be designed systematically, incorporating patient expectations and preferences in ways that provide the most streamlined end-to-end experience.	**Early patient engagement:** Don't overlook the importance of early consultation with patient-advocacy groups. This is another proven—yet often overlooked—way to gather in-depth insights that can help to ensure that the concerns, challenges, and capabilities of real patients and their care givers in a given therapeutic space are considered.
Early site engagement: Partnering with a CRO that has a diverse and experienced network of sites can inform efforts during protocol design and site selection.	**Balance the needs of trial and participants:** Reduce excessive or unnecessary blood draws, imaging procedures, and visits to clinical settings, balancing the needs of the trial with the needs of the participant, avoiding unnecessary endpoints to ensure that data gathering is not excessive or redundant.
Streamline excessive inclusion/exclusion criteria: Avoid ruling out the patients you want in the study, or including the wrong patients whose participation may undermine the clinical findings.	**Avoid denying access through inconsiderate protocol design:** Beware of poorly-considered protocols that may inadvertently deny access for specific patients. Certain individuals who otherwise fit the selection criteria may have specific needs or challenges that require special consideration.
Incorporate digital health techniques where possible: Look for ways to incorporate the use of telemedicine, patient-reported outcomes, and data from sensors.	**Develop educational materials that fit the population need:** During protocol design, stakeholders should explore alternative options for developing educational materials to ensure that they are most impactful for the broadest possible range of patients.

Sustainability goals can inform streamlined protocol development

It is axiomatic that if you create a trial protocol that optimizes efficiency, effectiveness, and productivity (by reducing unnecessary activities, streamlining processes, enabling telemedicine and other remote options for data collection, reducing testing requirements, and more), the trial will generate less waste. Therefore, designing protocols through the lens of carbon reduction promotes the efficiency of the trial design.

This carbon footprint calculation concept helps to inform the development of a more thoughtful protocol design and more efficient and less-wasteful trial execution. Many of the points mentioned above have an added benefit of lowering the study's carbon footprint, but additionally protocol designers should consider:

- **Efficiency of trial visits:** Minimizing the number of required site visits and maximizing the utility of each site visit
- **Efficiency of virtual visits:** Allowing for the use of virtual visits with clinicians to reduce travel and site visits
- **Efficiency of digital trial elements:** Enabling digital options that support at-home data collection as part of a BYOD strategy
- **Efficiency of kit supply:** Exploring the use of just-in-time kit delivery to help reduce the number of kits produced and shipped and to reduce disposal of wasted kits that are not ultimately needed
- **Efficiency of clinical supply chain:** Giving careful consideration to waste disposal and opting for redistribution and recycling of study supplies as part of the overall clinical supply chain where possible

Additional protocol pitfalls worth consideration

Trial design and conduct is complex and represents a critical and risky stage in the eventual introduction of new treatment options for patients in need. Having already outlined many of the key learnings towards protocol design, and patient- and site-centricity, a number of additional factors are worth noting to maximize success.

First is the need to design with the end in mind. With a strong focus on delivering trial data to satisfy the needs of regulators for marketing authorization, it's easy to overlook the commercial value of the investigational therapy. There is little value pursuing a marketing authorization if the commercial market for the product is not apparent. Ideally, developers should also assess the competitive landscape within the therapeutic space against prevailing standard of care and existing products approved for use in the therapy area, and design-in endpoints that help to generate data that is commercially compelling.

Another easily overlooked factor is a simple logistic one—having unrealistic or untenable trial logistical requirements. Working in collaboration with site partners, it makes sense to ensure that the quantity, storage requirements, and shelf-life of sample kits are appropriate for the expected patient volumes and clinic visits. Failure to do so could result in wasted patient visits and trial time lost.

Finally, country-specific factors can undermine progress in a global trial. Factors include local language requirements in educational materials, local language support for integrated digital health components, and cultural norms that can easily be overlooked when protocols are designed centrally without much thought given to the needs of varying regions. Time invested early in the protocol to master these regional differences can help to avoid protocol deviations and amendments later.

Consider all trial design models, as early as possible

Additional strategies are available to help streamline the trial's operational efficiency and potentially reduce the burden on patients and investigators. All options should be explored by drug sponsors and their CRO partners before the protocol is locked down. These include:

Adaptive trial designs. This option allows drug sponsors and their CRO partners to modify or adjust the trial decision points, dosing strategies or patient cohorts, or initiate additional study arms as interim data becomes available during the course of the trial. Such an approach can help to reduce the need for protocol amendments later by building in adaptable flexibility to protocols up front.

Pragmatic trial designs. This option is designed to test the effectiveness of the intervention in a broad, routine clinical setting or practice, in order to maximize the applicability and generalizability of the clinical findings.

Decentralized elements and hybrid trial models. The use of a decentralized or hybrid trial model makes greater use of remote monitoring, home health visits, telemedicine, the use of wearable devices, and patient reported outcomes (PRO) to ensure ongoing treatment and data collection, while reducing the frequency of patient visits to the clinical setting. Building such flexibility into the protocol can greatly reduce the burden on both patients and trial sites, which can help to reduce patient dropout and clinician burnout.

Studies and external control arms based on various forms of real-world data (RWD). Increasingly, RWD from various sources can help to inform and enrich the trial design and protocol development, by providing data-driven insights that are directly related to treatment pathways and disease progression, patient behaviors, adherence patterns, and clinical outcomes.[4]

Explore options for the appropriate use of artificial intelligence (AI), machine learning (ML), and related data-analytics and modeling methodologies. Such advanced capabilities can help stakeholders streamline and automate certain aspects the trial design and protocol, carry out modeling that can predict, for instance, the probability of success for the trial based on changing critical parameters, or which parts of the anticipated protocol design would have the greatest likelihood of impacting clinical outcomes.*

* The subject of using AI/ML tools to improve trial productivity is covered in depth in Chapter 2 of this productivity series **www.fortrea.com/insights**

Engage the CRO early for best results

With their broad and deep bench of experience, CRO partners can help carry out such critical assessments before and during protocol development. As a practical matter, it helps to bring an engineering mindset to bear. For example, one way to do this is to establish a firm constraint up front and then reverse engineer a process that could accommodate that constraint. For example, a productivity-oriented constraint may include such rules as: "This trial will provide no more than 50 ft^3 of supplies per patient," or "This trial will require no more than 15 hours of total participation time per patient." Such an exercise will help the team to design and operationalize a more practical and streamlined trial experience.

Drug developers have different preferences when it comes to how and when to engage a CRO to help with some or all of the trial design and execution. In some cases, the drug sponsor will develop the trial protocol on its own and engage the CRO later in the process—to essentially operationalize the trial with little or no input up front.

However, protocol development that relies solely on the drug sponsor's internal team members can lead to missed opportunities. Internal personnel may lack the broad experience, context, and economies of scale that could help to produce an optimized trial protocol as early as possible in the process.

Meanwhile, such an approach may fail to appropriately identify all of the complex requirements that impact different trial sites across the world or lack experience in all of the many opportunities that may be available to streamline the trial requirements (and thus optimize the protocol). Keep in mind that so often drug developers "don't know what they don't know" when it comes to how to optimize the protocol design with productivity goals in mind. This is particularly true for smaller, narrowly-focused companies and startups.

When the drug developer enlists a CRO much earlier in the process, that experienced partner will be directly involved in critical aspects of protocol design. It can draw upon its broad experience and expertise, and benchmark against best practices and proven strategies that have worked in specific therapeutic spaces and geographic regions. **Table 3** provides additional ways in which working with a CRO can directly improve trial protocol design.

Table 3.

What an experienced CRO brings to the table

Shown below are some of the ways in which an experienced CRO can directly impact and improve the trial protocol:

Start with the end in mind	• Help the drug sponsor assess the competitive landscape for the investigational therapy • Identify differences in the standard of care in different countries where the sponsor wants to establish trial sites (as these may influence the trial protocol and execution) • Identify the most appropriate primary and secondary endpoints (informed by real world data [RWD]-derived insights)
Prioritize patient- and site-centric design	• Conduct feasibility studies and adapt the trial protocol for optimal success (for instance, to create comparator arms, amend the inclusion/exclusion criteria, and more) • Develop tailored trial protocols for rare and orphan indications, working closely with patient advocacy groups, patient registries, and real-world data sources to address the particular needs and challenges of disease-specific patient cohorts targeted by the trial
Leverage an experienced global regulatory team	• Create a framework that explicitly supports the prevailing regulatory approval and product-launch objectives
Strive for operational efficiency	• Achieve efficiencies by utilizing a CRO's established infrastructure, streamlined processes, and experienced staffing models • Leverage sustainability concepts to highlight waste (which = inefficiency) • Leverage input from a CRO's global site network where protocols on paper become trials in practice
Serve as a connector for best-in-class sites, technologies and other partners	• Draw upon its existing experience and expertise and professional connections • Benefit from economies of scale with regard to staffing, partnerships, and technology infrastructure in different regions

Closing thoughts

Clinical trials are high-cost, high-stakes undertakings with the potential to deliver high-rewards to patients and sponsors. Stakeholders share many common goals—to identify and develop a steady stream of life-changing and lifesaving interventions across a broad array of therapeutic spaces. At the heart of every clinical trial is the trial protocol. Too often, insufficient attention to protocol development results in timeline delays, budget overruns, quality issues, recruitment and retention challenges and more. The actionable recommendations showcased in this article can help drug sponsors and their CRO partners to create trial protocols that more effectively identify and address issues that impact trial investigators and patients, and in doing so, create demonstrable productivity gains, and thus allow for greater clinical and commercial success. Such outcomes benefit all stakeholders.

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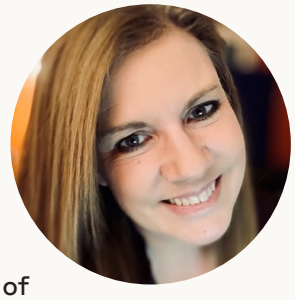

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Melissa has 24 years of industry experience dedicated to accelerating representative patient recruitment across all phases of clinical research. As Fortera's Global Head of Patient Recruitment and Engagement she works to harness the benefits of applying innovative solutions toward successful patient recruitment and retention campaigns while driving health literacy, diversity and inclusion and patient access equity to reduce study burden and facilitate enrollment into everyday life. Melissa also heads up Fortrea's Voice of Patient program to drive patient insights into every step of the drug development paradigm including protocol design and patient support programs.

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Clare Campbell-Cooper joined Fortrea in February 2020 and serves as its Global Head of Digital Health and Innovation. With more than 25 years of industry experience, Clare is a recognized leader within the field of digital health. She has a wealth of experience encompassing many disciplines within clinical research and has held management positions within Data Management, Clinical Monitoring, Phase I Operations, Strategy and Planning, Project Management and, most recently, Digital Health.

Clare is an active member on a number of boards and associations and sees that working in a pre-competitive environment is critical to helping drive change within the industry. Clare is passionate about how we can change clinical trials for the better and is a member of the Fortrea Environmental Sustainability Committee and a founding member of the Fortrea Sustainable Future Chapter. Clare sits on the Kings College London Scientific Advisory Board, Centre for Pharmaceutical Medicine Research, and is a visiting lecturer at KCL.

In her role as Global Head of Digital Health and Innovation at Fortrea, Clare is helping to change the face of how clinical research is developing. She specializes in strategy development for both internal and external partners. Clare's special interest lies in the relationship between the caregiver and physician team and how the use of digital technology can augment this.

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